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HEMADSORPTION VIRUSES IN INFECTIONS OF THE RESPIRATORY TRACT OF CHILDREN.
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(B)

HEMADSORPTION VIRUSES IN INFECTIONS OF THE RESPIRATORY TRACT OF CHILDREN

Preliminary Report

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In recent years at least eight viruses or groups of viruses other than influenza have been reported as possible causes of respiratory tract disease. Studies on many of these agents have not been large enough nor are there sufficient controlled epidemiological data from different times and places yet to be at all definitive about the frequency with which these viruses cause the illnesses concerned. The search, therefore, has continued for the agents responsible for a majority of respiratory illnesses.

In January of this year we reported two new myxoviruses, hemadsorption viruses types 1 and 2, which were isolated from children with respiratory disease.[1] This paper is to summarize information about these agents and to submit the results of controlled studies which indicate that these viruses play an etiological role in respiratory diseases of children.

METHODS

In these studies carried out jointly in the clinics and research laboratories of Children's Hospital and in the laboratories of the National Institutes of Health, material from the respiratory tract of infants and children with respiratory disease and from age-matched controls was placed in several tissue cultures. These included monkey-kidney, KB, human embryo fibroblasts, human heart, human liver and human amnion cells. In addition,

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FIG. 1. Adsorption of guinea-pig erythrocytes to monkey-kidney tissue culture in the presence of hemadsorption viruses (positive) and normal monkey-kidney tissue culture (negative). With the permission of the *NIH Record.*

the hemadsorption method of Vogel and Shelakov was utilized with the monkey-kidney tissue cultures. The patients under study were separated into two major groups, those with respiratory illness indicating hospitalization such as bronchopneumonia, bronchiolitis and croup, and those with less severe respiratory tract illnesses seen in the outpatient department. Age-matched control groups were available for each. In a majority of the patients who were hospitalized and in some outpatients serum samples were obtained from acute and convalescent phases of illness or equivalent periods of time in control patients.

VIRUS CHARACTERISTICS

In October 1957, shortly after this study was initiated, 2 patients' throat specimens produced an hemadsorption effect in tissue culture. This effect was determined not to be due to Asian influenza virus, which was prevalent at the time, nor to other influenza agents. Subsequently it was determined that this effect was a manifestation of two newly recognized myxoviruses, hemadsorption viruses types 1 and 2. Figure 1 shows normal monkey-kidney tissue culture and the hemadsorption effect in the presence of one of these new agents. These agents exhibit not only the property of hemadsorption but also produce hemagglutination by standard methods. A complement-fixing antigen has been prepared from monkey-kidney and KB tissue culture material. It has been possible with human, animal and fowl serums to utilize neutralization, complement-fixation, hemagglutination-

inhibition and hemadsorption-inhibition techniques for antigenic study. The characteristics of these viruses can be summarized as follows:

1) These agents are myxoviruses.

2) These agents are serologically distinct one from the other. Type specific rabbit serums react with the homologous type hemadsorption virus in hemagglutination-inhibition and neutralization tests. With human serums, however, the occurrence of a rise in complement-fixing antibody to type 2 virus is associated approximately 50 per cent of the time with a rise in titer to type 1. The reverse is not so. This indicates that the hemadsorption viruses, although distinct, do have some antigenic similarity.

3) These agents are distinct from other known human myxoviruses by antigenic analysis. Type 2 hemadsorption virus does possess a common complement-fixation antigen with Sendai virus but it can be distinguished from this agent by hemagglutination-inhibition and neutralization tests.

CLINICAL RESULTS

The first good evidence for association of hemadsorption viruses with respiratory tract disease came in November 1957. During an outbreak of respiratory disease in an orphanage nursery, type 1 hemadsorption virus was significantly associated with febrile respiratory tract illness. Table 1 shows the relation of hemadsorption viruses to respiratory tract disease in several hospital studies in the Washington, D. C. area for a six month period. Hemadsorption viruses 1 or 2 were isolated from 47, or 7.0 per cent, of 668 children with respiratory disease and from only 2, or 0.3 per cent, of 534 children without respiratory disease. This further indicates an etiological role for these viruses in respiratory illness. Such evidence is reflected in the group of patients from Children's Hospital. Table 2 analyzes the isolation rates in various illness and age groups. From these figures one can also observe:

TABLE 1

Association of Hemadsorption Viruses with Acute Respiratory Illness. October 1957–March 1958, Washington, D. C.

Hospital	Respiratory Illness				No Respiratory Illness			
	No. tested	No. isolations			No. tested	No. isolations		
		Type 1 hemad-sorp.	Type 2 hemad-sorp.	Total		Type 1 hemad-sorp.	Type 2 hemad-sorp.	Total
Children's Hosp.	548	13	26	39	427	1	1	2
D. C. General	110	4	3	7	103	0	0	0
Georgetown Univ.	10	1	0	1	4	0	0	0
Total	668	18	29	47	534	1	1	2

TABLE 2

Influence of Age upon Isolation of Hemadsorption Viruses. Children's Hospital, D. C., October 1957–March 1958

Age	Severe Respiratory Illness. Patients Hospitalized				Minor to Moderate Respiratory Illness. Patients Seen in Outpatient Clinic			
	No. tested	No. isolations			No. tested	No. isolations		
		Type 1	Type 2	Total		Type 1	Type 2	Total
years								
0–1	75	1	3	4 (5%)	106	4	12	16 (15%)
1–2	67	2	2	4 (6%)	61	1	3	4 (7%)
2–4	52	1	2	3 (6%)	67	1	2	3 (4%)
4–6	28	1		1 (3%)	47	1	2	3 (6%)
6–10	27				18	1		1 (6%)
Total....	249	5	7	12 (5%)	299	8	19	27 (9%)

Note: In the control group of 427 infants and children with non respiratory illness, 2 hemadsorption viruses (1 type 1 and 1 type 2) were isolated—an isolation of 0.47%.

1) a higher rate of isolation in patients with less severe illness, 9 per cent, than in those with respiratory illness requiring hospitalization, 5 per cent, suggesting that these agents are associated primarily with minor respiratory tract illness which may in certain instances progress to more serious disease.

2) a high rate of isolation in infants with less severe illness, 15 per cent, and a general trend toward lower rates after the age of 2. This may be only a minimal estimate of the contribution of hemadsorption viruses to illness in the infant group since many of these patients came to the hospital three to four days after onset of symptoms. The prevalence of isolations and rises in complement-fixing antibody to hemadsorption viruses 1 and 2 has remained relatively constant in the group under study for the period of time October through March, in sharp contrast to Asian influenza which was highly prevalent in October, disappeared and then recurred to an extent in late January and February.

Both types 1 and 2 hemadsorption viruses isolated in outpatients were associated in general with low grade fever, rhinorrhea, minimal pharyngeal erythema, dry cough and coarse breath sounds. Many such patients were said to have a common cold. They had been ill for two or three days before presenting at the hospital and rarely found it necessary to return for further care. Three of the hospitalized patients yielding hemadsorption virus type 1 had bronchopneumonia; 2 had severe bronchitis. From the study of serum specimens on admission and three weeks later by complement-fixation tests, these isolations were confirmed.

TABLE 3

Association of Type 2 Hemadsorption Virus with Croup Syndrome

Group	Type 2 Hemadsorption Virus Isolation			CF Antibody Rise for Type 2		
	No. tested	No. positive	% positive	No. tested	No. positive	% positive
Croup	33	6	18	27	9	33
Hospitalized—non croup respiratory	216	1	0.5	134	7	5
No respiratory illness	326	1	0.3	56	1	2

Even more striking is the association of type 2 hemadsorption virus with a croup syndrome (table 3). Of 35 patients with croup tested, type 2 hemadsorption virus was isolated from 18 per cent. Of 27 patients with croup whose acute and convalescent serums were available for study, 9, or 33 per cent, showed a rise in complement-fixing antibody for type 2 virus. These figures contrast strikingly with the isolation rate, 0.3 per cent, and antibody rise, 2.0 per cent, in control patients and other respiratory patients who did not have a croup syndrome. Type 2 virus was otherwise isolated from a hospital patient with pneumonia. Most of the patients with croup syndrome had been ill with cough, fever and rhinorrhea for three or four days before entering the hospital. One patient died following the complications of tracheostomy but in general the patients were not very "toxic" and the fever ranged around 102°F. Leukocytosis was not present.

We feel that these data suggest strongly that:

a) Hemadsorption viruses are etiologically related to infections of the respiratory tract in children.

b) Their association with illness is most prevalent in infants under the age of 1 year.

c) Type 2 hemadsorption virus may provoke a croup syndrome.

If this frequency of association is borne out in continuing and future studies, then hemadsorption viruses may be among the most prevalent causes of respiratory illness in children.

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BRONCHIOLITIS

William R. O'Reilly, M.D.*

Bronchiolitis may be described as an acute respiratory syndrome, usually occurring in infants under 2 years of age and characterized by rapid, labored respirations, audible wheezing, generalized obstructive emphysema, prostration and cyanosis.[1-4] More specifically, the term is a descriptive one, referring to the pathologic changes in those anatomical structures of the lung primarily affected, namely the bronchioles located between the large airways and the alveoli.

The initial publication dealing with bronchiolitis was written by Lange[5] in Germany in 1901. In the first quarter of this century, most published reports of the disease came from European centers, so that in 1934, Reichle and Moritz,[6] commenting on the paucity of communications about this subject in this country, stated, "American and English textbooks . . . have given no serious consideration (to this entity). Did we not know from our own work that it is seen rather frequently in the United States, we might imagine that it was peculiar to the continent of Europe and particularly to Germany where excellent descriptions have appeared in several textbooks."

Since that time innumerable articles dealing with this topic have appeared in British and American journals under a variety of titles, viz.: peribronchial pneumonia, subperibronchiolar pneumonia, capillary bronchitis, acute asthmatic bronchitis, interstitial bronchopneumonia, pneumonitis, primary pneumonitis and obstructive emphysema.

ETIOLOGY

The etiology of bronchiolitis, as yet, is unknown. Wood[7] and her coworkers isolated *Hemophilus influenzae*, types A and B, from a large percentage of nasopharyngeal aspirates from 51 patients with bronchiolitis. Earlier, Blake and Cecil[8] produced in monkeys pulmonary lesions quite similar to those found in bronchiolitic patients, with pure cultures of *H. influenzae*.

Other investigators[1, 9] however, have failed to demonstrate a significant predominance of one bacterial species over another from throat cultures of infants ill with this disease.

Some feel that a virus may be indicted as the prime etiologic agent. High[1] suggested that the finding of low normal leukocyte counts, a history of previous exposure to a viral disease (upper respiratory infection, common cold or primary atypical pneumonia) and the slow response to the administration of antibiotics seen in bronchiolitis may be signs indicative of a non-

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bacterial infection. Adams[10, 11] believed that a virus similar to the one which causes canine distemper in dogs may cause primary pneumonitis.

Hubble and Osborn[4] related the disease to infection with the influenza virus, while McCordock[12] experimentally produced mural bronchiolitis by placing canine distemper virus into the trachea of a dog and following it two days later with pyogenic bacteria.

INCIDENCE AND SEASONAL DISTRIBUTION

Bronchiolitis is almost always encountered during the winter and spring months and is almost universally seen in children under 2 years of age, although it may be found in adults.[13] In the latter group, it is usually superimposed on some chronic pulmonary disease such as chronic bronchitis, bronchiectasis, fibrosis, emphysema, asthma or combinations thereof. No known sex difference has been shown to exist and the patient's nutritional status does not appear to be an important factor in causation.[14]

CLINICAL MANIFESTATIONS

Acute bronchiolitis is usually preceded by a prodromal period during which the patient exhibits signs and symptoms suggestive of a mild upper respiratory tract infection or a common cold. These include anorexia, sneezing, coughing and particularly rhinorrhea. Diarrhea may be seen in 50 per cent of the patients.[2] Family history is usually noncontributory, and no higher frequency of allergy or chronic respiratory tract disease is noted in families of these patients.[2]

Following the prodromal period, which may be present for a variable length of time (a few days to a few weeks), there occurs a sudden change in the patient's condition, the mild constitutional symptoms becoming overshadowed by signs of marked respiratory distress.

The child, although alert, is apprehensive, irritable, often cyanotic when first seen, and in general, markedly and critically ill. Audible wheezing is present, respirations are shallow and rapid, and the respiratory rate may vary between 60 and 120 cycles per minute. The term "thoracic fibrillation" has been proposed by one of the residents at this hospital to describe the unique character of respiratory movements seen in these sick children.

Expiratory grunt, dry cough and tachycardia of a high degree are commonly encountered.

There is, quite frequently, little or no febrile response[1, 3, 14] but temperatures as high as 105°F.[2, 9] have been observed.

The most significant findings are noted in the chest. There is an increased anteroposterior chest diameter; the accessory muscles of respirations are actively used so that suprasternal and substernal retractions are visibly present. An extremely hyperresonant percussion note is heard, and dia-

phragmatic excursions are minimal. Because of the marked depression of the diaphragm, the thoracic cage may have the appearance of being in a continuous extreme inspiratory state.

By auscultation of the lung fields one discerns a marked prolongation of the expiratory phase. Rales may or may not be present; if present they may be either localized or widely distributed throughout both lungs.

Dehydration may be severe because of excessive water loss secondary to hyperventilation. Death may occur because of exhaustion, asphyxia and possibly cardiac failure.

LABORATORY FINDINGS

The leukocyte count is usually within normal limits[1, 3, 7] although some authors have observed a range between 5,100 and 31,000 per cu. mm.[9] Differential counts may show either a lymphocytic or polymorphonuclear preponderance; an absolute monocytosis has been reported[9] whereas an eosinophilia is rare.[15] Wood[7] and her colleagues observed that the leukocyte count is normal for the first two or three days of illness after which a relative lymphocytosis is demonstrable.

Urinalysis usually reveals no alteration from the normal; blood cultures are reported to be sterile by most authors, but Henderson and Rosensweig[9] obtained positive blood cultures from 36 bronchiolitic patients. In all but one, the isolated organism was *Staphylococcus aureus.*

Mild to moderate respiratory acidosis may be present, and although no one up to the present time has reported any serum electrolyte changes in children with bronchiolitis *per se,* Finberg and Harrison[16] noted hypernatremia in 8 infants under 2 years of age who had respiratory infections. These patients with infection but without diarrhea had restricted water intake, fever, and hyperventilation as prominent clinical features.

ROENTGENOGRAPHY

Paul[17] has written that the classical x-ray picture of bronchiolitis is one of uniform bilateral emphysema involving all portions of the lungs. The heart appears narrow, the diaphragm depressed, and there is no appreciable mediastinal shift. Some feel that radiographic evidence of bronchiolitis is manifested by other roentgenologic findings, existing either alone or in combination.[3, 18] These include increased bronchovascular markings with varying degrees of peribronchial infiltration, bulging of the emphysematous lung tissue into the interspaces, multiple small areas of emphysema surrounded by normal or partially atelectatic lung tissue, and mild degrees of consolidation or collapse. It is interesting to observe, however, that in a series of 68 cases of bronchiolitis reported by Gans,[18] two-thirds of the x-ray films were reported as being normal. Fluoroscopic exam-

ination, although deceptive because of the bright appearance of the lung fields, is of aid to correct interpretation.[3]

CARDIAC FAILURE

Whether or not cardiac failure occurs in children with bronchiolitis has been a subject of debate for many years. Pratt[2] mentioned that hepatosplenomegaly may be due to passive congestion secondary to circulatory failure. In contrast is the statement of High[1] that "emphysema may be so marked that the liver and spleen can be palpated several centimeters below the costal margin." Cohen[19] used as his criteria for the presence of failure the findings of increased pulse rate and increased liver size, and considered 8 of 319 patients to be in cardiac failure. One important point that he noted from the charts he reviewed was the fact that sudden increase of liver size was not necessarily accompanied by increasing emphysema or dyspnea. Therefore he did not attribute progressive hepatomegaly to diaphragmatic depression alone.

In one series,[9] 45 of 457 patients showed abnormal electrocardiographic changes such as abnormal rhythm, frequent extrasystoles, abnormal QRS pattern and low amplitude, and inversion or notching of the T waves. All 45 patients were felt to show clinical evidence of cardiac failure, and in all, the EKG changes were reversible. Interestingly, in the same series other patients with other infections showed the same type of electrocardiographic pattern.

MORTALITY RATES AND RECURRENCE

In documented reports appearing in the literature up to the present time, the mortality rates have ranged from less than 1 per cent to 25 per cent.[1, 4, 9, 15, 18] Recurrences of bronchiolitis in the same patients are unusual.

TREATMENT

In general, treatment of bronchiolitis is supportive and symptomatic. The use of wide spectrum antibiotics has been advocated by some[1, 3, 4] but questioned by others.[9] However, this author feels that the use of antibacterial agents in hospitalized patients is justified to prevent secondary bacterial infection from supervening.

Administration of humidified oxygen is universally accepted as being of prime importance in treatment. In our experience, the addition of wetting agents as aerosols in treatment has not hastened clinical improvement. In severely sick children, fluid intake must be maintained by parenteral administration of appropriate solutions.

Further investigation regarding the use of steroids, antihistamines,

adrenaline and bronchoscopy in treating bronchiolitic patients must be forthcoming before they are incorporated wholeheartedly in the therapeutic regimen of bronchiolitis.

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CRANIOSTENOSIS

Pio G. Vera Cruz, M.D.*

Craniostenosis is the premature and abnormal fusion (synostosis) of two or more membranous bones of the cranial vault, producing a variety of deformities of the head and resulting in mechanical limitation of normal brain growth during infancy.

Normally, only the suture between the two frontal bones (metopic) fuses before birth or during the first few years of life, although occasionally it persists for a longer period. The serrated margins of the bones of the vault interlock at the end of the first year causing apparent closure of the sutures, but x-ray examination discloses that there is no actual fusion of the bones. During this period, growth of the skull, which corresponds normally with that of the brain, is feasible because of the existence of the suture spaces. The posterior fontanelle closes by the second month and the anterior fontanelle between the tenth and sixteenth months. Ordinarily the brain accomplishes about 50 per cent of its postnatal growth during the first year of life, 25 per cent more by three years, and by the end of the seventh year it has completed 90 per cent of its entire growth. Obliteration of the suture line begins when the period of growth has terminated for the most part, the coronal suture being the first, then the sagittal, and finally, the lambdoidal suture. Not until the third or fourth decade, or even later, does complete disappearance of the suture lines on the external surface occur. Because of the close interrelationship between the growth of the brain and of the skull, craniostenosis assumes a practical importance when it develops during the intra-uterine period or first year of life. The mechanical nature of the condition and the apparent absence of primary pathology in the nervous system, make surgical therapy the only treatment for this lesion. Early recognition of craniostenosis and its prompt correction by operative intervention is, therefore, imperative. In the case to be presented, early detection and immediate corrective procedure may have prevented the sequelae of craniostenosis which presumably would have developed.

CASE REPORT

The patient, a 10 week old white male infant, was admitted for the first time to Children's Hospital on October 15, 1956, because of early closure of the fontanelles. Following an uneventful full term gestation, the infant was born by frank breech delivery with a birth weight of 7 pounds 6 ounces, and measuring 19½ inches in length. The circumference of the head was 33 cm. and the various diameters measured as follows: biparietal, 9.5 cm.; suboccipitobregmatic, 9.5 cm.; occipitofrontal, 11 cm.; and occipitomental, 10 cm. He cried spontaneously after birth and no difficulties were encountered during the neonatal period. There were no feeding problems, and

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FIG. 1A. P-A view of skull. Premature closure of sagittal and coronal sutures leading to vertical enlargement of the head: scaphocephaly. The lambdoidal sutures remain open.

growth and development had been normal. At the age of 10 weeks the infant could smile, coo and lift his head while in the prone position. During the routine six week check-up the private physician observed closure of the fontanelles. Subsequent x-ray examination of the skull showed complete closure of the posterior fontanelle and partial closure of the anterior fontanelle. The child had been doing well except for a left middle ear infection at the time of his check-up and slight anorexia during the two days prior to admission.

The family history revealed the father, mother and three siblings to be all living and well. The second and third pregnancies of the mother terminated in miscarriages. The paternal grandfather had cancer and heart disease, and the paternal grandmother also had the latter ailment.

Physical examination on admission showed a well developed, well nourished infant in no distress. He weighed 10 pounds 15 ounces, had a temperature of 100°F., pulse rate of 110 per minute and respiratory rate of 24 per minute. The circumference of the head was 39 cm., and of the chest 39.5 cm. There was slight asymmetry of the head in that it was slightly depressed on the left parietal area and showed a slight prominence of the frontal bone on the same side. The posterior fontanelle was closed, but the anterior was open 0.5 by 0.5 cm. No sutures were palpated. The eyes and throat were normal. A ruptured furuncle was seen in the left external auditory canal, but the right ear was normal. Scanty mucous nasal discharge was present. The neck and chest were unremarkable, and the lungs and heart were normal to percussion and

FIG. 1B. Lateral view of skull. Same case as figure 1A.

auscultation. The abdomen and extremities were normal. The external genitalia were those of a normal circumcised male infant, with both testes descended. The neurological examination showed physiological findings.

Routine examination of the blood and urine were within normal limits. Roentgenographic examination of the skull disclosed complete closure of the posterior fontanelle, and almost complete obliteration of the anterior fontanelle. All sutures were faintly visible, and a depressed fracture was visualized in the left parietal bone. A ventriculogram revealed a normal ventricular system, and an area of air over the left frontal lobe. Tuberculin test was negative.

After the ear infection had been treated, cranioplasty was performed on October 23. Complete dissection of the coronal suture and partial dissection of the temporosquamous sutures were done, and a bilateral longitudinal dissection was made along the sagittal sinus, 1 inch lateral from the midline, and extending posteriorly to the lambdoid sutures. Polyethylene sheets, used to cover the bone edges, were sutured to the bones. The postoperative course was uneventful, and the patient was discharged, improved, on the eighteenth hospital day.

He has been checked regularly in the Neurology Clinic. Growth and development have progressed normally, and the child has remained asymptomatic. When last seen, at the age of 18 months, the circumference of the head was 46.5 cm., and skull x-ray showed good visualization of the coronal and sagittal sutures.

DISCUSSION

In 1839 Somering referred to the relationship between the premature closure of certain skull sutures and head deformity. It was not, however, until 1851 that a scientific explanation of cranial deformities was presented for the first time by Virchow. He introduced the term craniostenosis and postulated that premature fusion of the sutures was the direct cause of

restriction of growth of the skull, and, therefore, the primary cause of cranial deformities. He also formulated the principle that when premature synostosis of two bones occurs, normal growth is inhibited in a direction perpendicular to the obliterated suture line producing compensatory growth in other directions.

Although the majority of cases are found in isolated instances, an hereditary factor is suggested by many reports of craniostenosis appearing in siblings and in more than one generation in a family. There is also frequent association with hereditary or congenital stigmata. No definite racial influence has been observed, although it has been mentioned that scaphocephaly seems more common among Negroes. There is a greater incidence in males (85 per cent of cases), than in females, but Rubin has suggested the possibility that its frequency in the female, especially in its mild form, may be concealed by long hair. Craniostenosis is not a rare condition. Ingraham and his group reported 50 cases in their series; Koziak collected 22; King and his group reported 17; Mount and Howell presented 6 and 3 cases respectively. Abnormal fusion may occur before birth or during the first months of life; in the latter instance the resulting deformity is usually minimal.

Several theories have been advanced regarding the etiology of craniostenosis. Virchow thought that it might be due to some form of meningitis appearing in the cranial membranes of the fetus. In 1875, Morselli suggested that too close a proximity of the ossification centers of adjoining bones caused the premature fusion. Rieping and Greene independently noted the abnormal placing of the centers of ossification. Park and Powers, in 1920, pointed out that the defect is in the germ plasm, producing abnormalities in the interstitial mesenchyme which causes failure of new bone growth, a process which then promotes early calcification of the suture lines. In 1935, Mann offered the theory that the whole condition is of germinal origin, and that it is due to mesodermal failure within the bones of the skull, resulting in a reversion to an atavistic type. Many authors are of the opinion that the last two hypotheses are the most feasible.

Depending on the sutures involved the following terms have been used: 1. oxycephaly (syn.: acrocephaly, tower-skull, steeple-head, Türmschadel, turritum caput, turricephaly)—premature union of all sutures preventing normal expansion both in the transverse and anteroposterior directions; 2. brachycephaly—synostosis of the coronal suture restricting normal growth in the anteroposterior direction, and producing a broad and short head; 3. scaphocephaly (boat-shaped or keel-shaped head)—premature closure of the sagittal suture with compensatory lengthening of the skull in its anteroposterior diameter, and often widening and elevation of the

frontal region; and 4. plagiocephaly—premature union of the sutures in one half of the head and a compensatory development in the other half.

Some entities associated with craniostenosis include craniofacial dysostosis (Crouzon's disease) which constitutes stenosis of the cranial sutures and hypoplasia of the facial bones, and Apert's disease or acrocephalosyndactyly. In Ingraham's series of 50, the sagittal suture was involved in 29, and the coronal in 8; 4 had synostosis of both the sagittal and coronal sutures, 3 of the sagittal and lambdoid sutures, and 6 had involvement of all cranial sutures.

Various classifications of craniostenosis have been made by several writers, but as yet there is no general acceptance of any one arrangement. In 1926 Grieg classified cranial deformities, considering oxycephaly as a whole and dividing it into three types: 1. true oxycephaly which presents a general craniofacial stenosis, and which is congenital and often associated with syndactylism or other deformities of the extremities; 2. delayed oxycephaly which appears at any time during childhood and never presents other deformities; and 3. false oxycephaly which is localized synostosis, not congenital, and is often of definite origin. Fairman and Horrax, in 1949, suggested the following classification:

- Craniostenosis
  - Incomplete
    - Scaphocephaly
      - Compensated
      - Decompensated
    - Brachycephaly
      - Compensated
      - Decompensated
  - Complete
    - Oxycephaly
      - Compensated
      - Decompensated

They postulated that craniostenosis is decompensated when the patient shows signs of chronic increased intracranial pressure manifested by headache, vomiting, papilledema, failing vision, and convulsive seizures.

Koziak stressed that interlocking of the cranial bones does not inhibit growth at the site of interlocking but fusion seemingly does. When the capacity of the skull to increase in size is lost, with normal growth stimulus, intracranial pressure consequently rises; various compensatory mechanisms may occur, among which are separation or overgrowth of the nonsynostosed sutures, bulging of the thin skull bones with formation of a boss, and depression of the fossae, especially the middle and posterior, causing an increase in the vertical diameter of the cranial vault. Flattening of the orbital plates may also result from the expanding pressure, giving rise to exophthalmos. Signs of decompensation become evident when there is inadequate compensation following secondary bony changes of the skull.

As a rule the general health is unimpaired. It is apparent that the earlier

the onset of premature fusion of the cranial sutures occurs, the more likely is damage to ensue. While skull deformity is one of the characteristic features of craniostenosis, it may not be pronounced, or may even be absent, especially during the neonatal period. Palpation of a ridge along the closed suture, with no movement of adjacent bones, should arouse suspicion of this condition. It goes without saying that intracranial pressure is not as likely to be increased in the incomplete forms of craniostenosis as in complete oxycephaly. The symptomatology of this condition is characteristic of that of increased intracranial pressure, which has been reported to reach as high as 500 mm. of water, when expansion of the skull can no longer keep up with increasing brain growth. Mental retardation and blindness are the most serious complications, and although they develop most often in oxycephaly they may be present in varying frequencies in the other types. Among Ingraham's 29 cases of scaphocephaly, 7 had subnormal mentality. It is felt that blindness will not appear at all if it does not develop before 8 years of age. Optic atrophy is now generally believed to be due to compression of the optic nerve within the flattened optic canals, or to pressure alone, or to a combination of both factors. Other eye findings include strabismus, widening of the palpebral fissure, and proptosis. Anosmia and psychic anomalies have been described concomitant with craniostenosis. As a result of premature synostosis of the facial bones, hypertelorism, a high-arching narrow hard palate, and hypoplasia of the bones of the face and orbit may be encountered.

There are a number of apparently unrelated congenital anomalies that have been reported in association with premature union of the cranial sutures. Among these are varying degrees of syndactylism, hexadactylism, parietal bone defects, cleft palate, harelip, pigment anomalies of the retina, night blindness, dystrophia adiposogenitalis, congenital heart disease, spina bifida and meningocoele. Hereditary hemolytic jaundice has also been described with craniostenosis.

Points to be observed in roentgenographic examination of the skull in which the presence of craniostenosis is suspected are: 1. the shape of the skull, including its height, shortness, width, and deformities; 2. obliteration, either partial or total, of one or more sutures; 3. thinning of the skull with marked imprint of the cerebral convolutions; 4. convolutional atrophy; 5. alterations in the base of the fossae; and 6. underdevelopment of the sinuses. Figures 1A and 1B demonstrate the skull deformity produced by premature closure of sagittal and coronal sutures.

Because of the vast differences in treatment and prognosis, craniostenosis should not be confused with microcephaly, where the primary difficulty lies in the failure of the brain to grow. Head deformities, likewise, may

be produced by prolonged dependent positions. The extreme skull deformity and bizarre facies of some cases of craniostenosis may lead one to consider gargoylism (Hurler's disease), but the multiple tissue involvement of the latter is well known.

Being a correctable congenital deformity, the only treatment is, of course, operative. Surgery is directed at prevention of symptoms of increased intracranial pressure and their sequelae, correction of skull deformity, and relief of intracranial hypertension and restriction of brain growth. Optimum results of treatment, as to be expected, are obtained when surgical intervention is effected during the first year of life when rate of brain growth is at a maximum. The operation of choice is linear craniotomy with wrapping of polyethylene film over the cut edges of bone to retard closure of the craniotomy opening.

Prognosis for mental development and good visual acuity in patients treated under 1 year of age is excellent. If there has already been some loss of vision, it may be prevented from progressing further. It is important however, that periodic physical examinations and skull x-rays be done within one or two years after surgery, since some patients who have been observed over several years have shown gradual closure of cranial sutures other than those originally involved.

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THE EDITOR'S COLUMN

GAMMA GLOBULIN

In this day of modern medicine one can scarcely read an article concerned with the therapy of a bacterial or viral disease without finding some reference to the use of gamma globulin. While many of these recommendations are based on solid experimental and epidemiological evidence, many others are offered empirically in the hope that it "might do the patient good and will certainly do no harm." This attitude is hardly in keeping with today's emphasis on scientific medicine and encourages a needless waste of valuable human resources. In addition, allergic reactions to the intramuscular injection of gamma globulin, while unusual, do occur.

In the normal adult, there is a total of approximately 50 Gm. of gamma globulin, equally distributed in the intravascular and extravascular spaces.[1] This gamma globulin consists largely of antibody-carrying immunoproteins but also a considerable quantity of "nonspecific" gamma globulin of unknown function. The serum level of gamma globulin does not normally differ in the pregnant mother at term, her newborn infant, or the normal adult, levels of each approximating 1.20 Gm. per 100 ml. Immediately after birth, however, the serum level of gamma globulin in the infant falls gradually to reach lowest mean levels at three to four months of age (0.50 Gm. per 100 ml.) and thereafter slowly rises to approximate adult levels by three to five years of age.[2]

In the past, a great deal of concern has been expressed over relatively small changes in the gamma globulin fraction of serum determined by fairly crude methods. In a recent study,[3] serum gamma globulin levels were determined in a large group of children suffering from various bacterial and viral infections, and "hypersensitivity" diseases, together with another group of children with histories of repeated infections. In this series, the authors were unable to correlate any diagnostic or prognostic criteria for any illness with alterations in the serum gamma globulin level. Unless the physician is dealing with the markedly lowered level of serum gamma globulin found in patients with congenital or acquired hypogamma-

globulinemia, any isolated determination of the serum gamma globulin provides no useful information and is of no benefit to the patient.

Markedly low serum levels of gamma globulin are sometimes found in patients with malnutrition, chronic liver disease, or chronic kidney disease (nephrotic syndrome) in which there is impaired production or increased loss of the total serum proteins, among which is included the gamma globulin fraction. It has long been observed that under these circumstances, the patient contracts infectious diseases easily, and recovers from them with difficulty.

Much recent publicity has been directed toward the relatively newly discovered entity, congenital or acquired hypogammaglobulinemia, a disease marked by extreme susceptibility to infection, low to undetectable levels of both circulating antibodies and gamma globulin, immunologic unresponsiveness to antigenic challenge, and marked clinical improvement with replacement gamma globulin therapy. Frequently, a dose of gamma globulin of 0.1 Gm. per Kg. of body weight will afford quite satisfactory protection against repeated infection. Depending on the method used, gamma globulin injected into the body has a half-life of from 14 to 20 days or 25 to 30 days. In any event, gamma globulin replacement therapy should probably be repeated every three to four weeks. In those individuals with congenital or acquired hypogammaglobulinemia who do not respond to this regimen, a quantity of gamma globulin sufficient to raise the serum level at least 0.10 to 0.15 Gm. per 100 ml. higher than pretreatment levels is indicated.[4] Gamma globulin should never be given intravenously since severe hypotensive reactions invariably occur, but instead should always be administered by deep intramuscular injection; local reaction, with the exception of moderately severe discomfort, is usually mild.

Gamma globulin is commonly given to large numbers of patients in the expectation that its antibody content will provide passive immunization against one of a considerable number of common infectious diseases. Probably the most generally agreed upon indication for the use of gamma globulin is in preventing or attenuating measles infection.[5] Complete temporary protection of susceptible individuals exposed to measles is attained by the administration, between the third and eighth days after exposure, of 0.1 ml. of ordinary pooled gamma globulin per pound of body weight. Such protection should probably be given to infants under 12 months of age, children ill with other acute or chronic diseases, healthy children whose siblings are ill with other diseases or in institutional epidemics.[6] Immunity, though complete, rarely lasts longer than three weeks.

In children under three years of age in whom the mortality rate from measles is somewhat higher, and perhaps in older children, 0.02 ml. of

gamma globulin per pound of body weight administered during the first week of the incubation period will attenuate the infection. Such attenuated infection is mild and is accompanied by a much lesser incidence of complications, yet commonly produces a lasting immunity comparable to that produced by unattenuated disease.

Odessky and co-workers[7] have advocated massive doses of gamma globulin to be given to patients with measles complicated by measles encephalitis in the hope of reducing both mortality and morbidity. Allen and Frank,[8] however, in a controlled series and using a minimal total dose of 2.2 ml. of gamma globulin per Kg. of body weight and giving at least 30 ml. over a period of 36 to 48 hours, could not demonstrate any decided therapeutic advantage to this regimen. In both series, there was a somewhat lower mortality rate in treated individuals but the relatively small number of cases casts doubt on the statistical significance of this finding. It is generally agreed, however, that there is a very low incidence of complicating measles encephalitis in attenuated measles.

Following the initial report of Stokes and Neefe,[9] pooled gamma globulin has been used rather widely and successfully in the prevention of secondary attacks of infectious hepatitis in those persons exposed to infected individuals. Ashley,[10] using a dose of 0.01 ml. per pound of body weight to protect household contacts, found a secondary attack rate of 16.8 per cent in contacts not inoculated and only 1.1 per cent in inoculated contacts. Even though gamma globulin is of great value in the prevention of this disease, practical use is probably limited to institutional or camp outbreaks or in families in which a member has already contracted the disease.[11] Its use is further limited by the frequent failure to recognize infectious hepatitis occurring in the absence of jaundice. Recommended doses in various studies have ranged from 0.01 to 0.06 ml. per pound of body weight. After the onset of the disease, gamma globulin is of no value.

In view of the observation that gamma globulin has sometimes protected against clinical infectious hepatitis for a much longer period of time than would seem possible if only passive transfer of antibody were involved, recent interest has centered around the question of "passive-active" immunity resulting from clinically inapparent infection.[12] Wehrle and Hammon,[13] however, in investigating recipients of either gamma globulin or gelatin during the poliomyelitis field studies of 1951 and 1952, found a comparable incidence of hepatitis occurring in the five succeeding years in both groups.

Gamma globulin is not a vehicle for the virus of homologous serum hepatitis and is of no value in prophylaxis of this disease.

During nationwide field trials, pooled gamma globulin was shown to have some effect as a prophylactic agent against poliomyelitis.[14] Gamma

globulin was shown to modify the severity of poliomyelitis occurring within one week following prophylactic administration, to prevent the disease in a large percentage of cases from the second to the fifth week, and to exert a gradually diminishing preventive effect from the sixth to eighth week. Sabin,[15] however, has commented that since 80 per cent of secondary household cases of poliomyelitis occur within seven days after the first clinically diagnosed case, a period during which gamma globulin had been shown not to produce adequate prophylaxis, and since in 95 per cent of households, there are no clinically recognizable secondary cases of poliomyelitis, the procedure of administering gamma globulin to household contacts would still miss more than 90 per cent of the people who will subsequently develop poliomyelitis. The Committee on the Control of Infectious Diseases of the American Academy of Pediatrics recommends that gamma globulin, because of its rather dubious value in preventing poliomyelitis, not be given as a routine procedure to provide passive immunity against this disease.[16]

The use of gamma globulin in pregnant women exposed to rubella is still the subject of controversy. There is certainly no longer any doubt that this disease is responsible for the production of certain serious congenital anomalies in the fetus. Lundström[17] has shown that there is a 9 to 12 per cent incidence of fetal congenital anomaly if the mother develops rubella during the first trimester of pregnancy. That this is the critical period is also shown by the fact that he found only 1 to 3 per cent incidence of congenital anomalies in infants whose mothers contracted rubella during the second trimester and no incidence in infants whose mothers contracted the disease in the third trimester. In a large control group included in this study, only 1.6 per cent of infants were born with comparable congenital anomalies.

In a recent small but excellently controlled study, Krugman and Ward[18] have rather conclusively shown that gamma globulin is indeed of use in preventing rubella in susceptible children. They mixed serum containing active rubella virus with ordinary pooled gamma globulin, convalescent phase rubella plasma, convalescent phase rubella gamma globulin and normal human serum respectively, and injected one of each mixture into separate groups of six presumably susceptible children. Five of six children who received the virus-normal human serum mixture developed rubella whereas only one of six of each group receiving the virus-gamma globulin and virus-convalescent phase plasma developed clinically diagnosable rubella. None of the six children receiving the virus-rubella convalescent gamma globulin mixture contracted rubella. These results would be most interesting if they could be effected for pregnant women exposed to rubella. The question would remain, in theory at least, whether clini-

cally undiagnosable rubella is capable of exerting a deleterious effect on the human fetus. The authors caution, however, that since gamma globulin is prepared from pooled adult plasma, it will reflect the immune status of the donor. Certainly the concentration of rubella antibody in gamma globulin is lower than that of measles antibody. Krugman and Ward recommend a dose of gamma globulin of 0.15 to 0.20 ml. per pound of body weight to prevent rubella. For women exposed during pregnancy, an intramuscular dose of 20 ml. of gamma globulin or 10 ml. of convalescent phase rubella gamma globulin is suggested.

It is generally agreed that normal human serum gamma globulin is without value in protecting the susceptible exposed human against contracting mumps.[19] Mumps hyperimmune gamma globulin probably has a protective effect but at best it is unreliable. Factors which make evaluation of any therapeutic agent in mumps difficult include the relatively low communicability of mumps and the high incidence of previously undiagnosed subclinical infection. Since mumps is a relatively mild and uncomplicated disease in childhood, children exposed to the disease should be allowed to develop it.

The use of mumps hyperimmune gamma globulin, although without value in the treatment of mumps infection, should probably be given, in a dose of 20 ml. intramuscularly soon after exposure, to adults who do not demonstrate a positive cutaneous reaction to mumps antigen.[20] This is recommended in the hope that it might produce a transient state of immunity or decrease the likelihood of extra-parotid mumps infection. Any degree of passive immunity produced by hyperimmune serum, however, is of short duration and is probably no longer than the two to four week incubation period of mumps.

Pertussis hyperimmune gamma globulin in a dose of 2.5 ml. every other day for a total of 7.5 to 12.5 ml. is recommended for children, particularly infants severely ill with pertussis.[21] This recommendation is probably not based on very sound evidence, since most controlled studies fail to show any real effect of this agent on the duration or the clinical course of pertussis.[22, 23] All investigators admit that the evaluation of any single therapeutic agent is extremely difficult because of the marked natural variation of the disease. Pertussis hyperimmune gamma globulin (2.5 ml. intramuscularly, repeated in 5 to 7 days) has also been recommended for exposed susceptibles who have not had prior active immunization.[21]

Hyperimmune vaccinal gamma globulin prepared from recently vaccinated blood donors has been found useful and is recommended for intimate exposure to smallpox and for the prophylaxis and therapy of the serious skin complications of smallpox vaccination.[24] Administration of this hyperimmune gamma globulin 12 to 24 hours after either primary or

repeat vaccination does not interfere with the development of active immunity. Recommended prophylactic dose against smallpox is 0.2 ml. per pound of body weight in adults, 0.05 ml. per pound in children and 0.1 to 0.2 ml. per pound in infants under one year of age. Hyperimmune vaccinal gamma globulin in a dose of 0.6 ml. per Kg. also affords a high degree of protection to those children with eczema who require vaccination and to those children with eczema whose siblings are vaccinated. Hyperimmune gamma globulin is also of value in therapy of the severe complications of vaccination, i.e., eczema vaccination, generalized vaccinia and vaccinia gangrenosa.

Much recent discussion has arisen concerning the use of gamma globulin in antibiotic-resistant infections. Experimentally, in the mouse, a great deal of evidence has accumulated demonstrating that gamma globulin-chloramphenicol-protected mice had a markedly greater survival rate than mice protected with either gamma globulin or chloramphenicol alone. The effect was noted to be synergistic; against some strains of *Micrococcus pyogenes var. aureus*, the potentiation was 18 to 50 fold.[25] Potentiation was also present, although to a much less marked degree, in protected mice exposed to infection with Streptococcus, Pseudomonas, and Proteus. These experiments were extended to mice infected with *Diplococcus pneumoniae*, *Escherichia coli*, and *Salmonella typhimurium*. Again, considerably greater than additive effects were obtained.[26] When, however, prior to the experiment, the gamma globulin was incubated with the organisms to be tested, gamma globulin lost this potentiating effect, illustrating that it was not due to the gamma globulin *per se* but instead to the specific antibody content of the gamma globulin.[27]

Attempts to reproduce these experiments in man however, have been considerably less rewarding. Uncontrolled studies advocating the use of gamma globulin in infections in premature infants,[28] and in adults with refractory infections,[29, 30] are suggestive but far from convincing. The difficulties in setting up a properly controlled series would seem to be enormous.

It has long been a general impression that children with asthma are prone to respiratory infection. This increased susceptibility to infection is frequently hypothesized to be due to a "qualitative" defect in antibody production, since gamma globulin levels in asthmatic children are rarely below normal range.[31] The use of gamma globulin empirically in monthly doses during the colder months for prevention of the asthmatic attack associated with a respiratory infection in the child is rather widespread,[32, 33, 34] but the subject of some controversy. No doubt complicating the problem is the variability of the asthmatic attack and the uncertainty as to what constitutes an upper respiratory tract infection in the asthmatic

child. Glaser and Smelzer[35] point out that it is frequently difficult to ascribe the symptoms of a "cold"—sneezing, and nasal discharge and obstruction—to an infectious or allergic origin.

Abernathy and co-workers[36] in a recent well controlled study gave 0.6 ml. of gamma globulin per Kg. of body weight monthly to a series of asthmatic children. They could find no differences in response between the group who received this medication and the control group who received only normal saline. However, the entire study group consisted of only 22 subjects and the gamma globulin was administered for only a six month period. A further elaboration of a study such as this seems warranted.

It seems certain that gamma globulin is a very useful therapeutic tool in everyday medical practice. We would hope, however, that more discriminate and judicious care in prescribing this medication will limit its use to disease entities where it has definite value.

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